MEMORANDUM

DATE: February 6, 2001

TO: Members, Peripheral and Central Nervous Systems Drugs Advisory Committee and Invited Guests

FROM: Staff
Division of Neuropharmacological Drug Products

SUBJECT: Background Document for PCNS Meeting of March 14, 2001: Issues Related to the Development of Treatment for Vascular Dementia

1 Background

As you know, a meeting of the Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration will be held on March 14, 2001 to discuss the entity of Vascular Dementia. This paper has been prepared in an effort to brief you on the specific issues that we believe need to be addressed by the Agency when considering the regulation of drugs being developed to treat this putative clinical entity. In addition to this memo, we are forwarding a number of articles from the literature addressing several important aspects of this issue, which we hope will provide a more detailed background for the meeting.

1.1 Purpose Of Meeting

The purpose of this Advisory Committee meeting is to achieve a consensus on a number of issues related to the proposed entity of Vascular Dementia. These issues, which are discussed further below, are being raised in the context of the development of drugs intended for the treatment of that putative disorder.

1.2 Vascular Dementia

The term “vascular dementia” is commonly used in clinical practice to describe a putative clinical entity in which it is believed that cognitive impairment sufficient to impair functional abilities results from cerebrovascular disease causing brain infarction; “multi-infarct dementia” is also a term that has been proposed for the same entity. The types of infarcts that have been postulated to lead to vascular dementia are reported to fall into one or more of the following categories

- Multiple cortical infarcts secondary to atherosclerosis of the large cervical and intracranial vessels, or to cardioembolism
- Subcortical infarcts due to small vessel disease
- Single strategically placed infarcts that implicate areas that are important for cognition

Cerebral white matter changes, believed to be due to cerebrovascular disease, but which are often considered to fall short of frank infarction, have also be proposed as a possible mechanism for vascular dementia. Such white matter changes have been increasingly evident with the advent of modern brain imaging techniques such as high-resolution computerized tomography, and magnetic resonance imaging.

Despite the seemingly widespread acceptance of vascular dementia as an entity in routine clinical practice, there is still considerable controversy as to whether that putative disorder represents a distinct clinical syndrome, as further discussed in Section 2.

1.3 FDA Role

The FDA approves a drug for marketing based on a determination that such a treatment is both effective and safe, when used to treat one or more specific clinical entities. The entity for which such a treatment is intended, is referred to as the “claim” or “indication” for that drug and is described in the “Indications and Usage” section of the label. Proposed labeling must accompany the New Drug Application (NDA) submitted by the sponsor.

The Federal Food, Drug, and Cosmetic Act (the Act) requires that the approval of a drug treatment for a specific condition be supported by (among other things) “…substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling…”. Substantial evidence is further defined as evidence from “adequate and well controlled…clinical investigations…”. These definitions make clear that approval of a drug product is inextricably linked to our ability to adequately describe the population for whom the drug is intended and the drug’s effects in that population in labeling.

In order to do this, the following must generally be true:

- The condition can be defined without ambiguity using criteria that have wide acceptance, and are both valid and reliable
- Appropriate instruments be used for measurement of the clinical effect of the drug on that condition; such instruments must measure what they are intended to under the conditions under which they are actively employed
- Clinical trials should be appropriately designed to measure that effect
- The effect measured should be clinically meaningful

For the most part, 2 classes of clinical entities are considered appropriate for new drug claims

- Specific diseases or clinical syndromes, such as multiple sclerosis or chronic renal failure.
- Non-specific symptoms such as pain or urinary frequency

On occasion, claims may be also be directed at symptoms of specific diseases, e.g., excessive daytime sleepiness associated with narcolepsy.

The Act also states that the Secretary may refuse to approve an application "if based on a fair evaluation of all material facts, such labeling is false or misleading." Labeling that states that a particular drug is indicated for the treatment of a specific clinical entity could be considered misleading if the condition if not well-defined, the effect of the drug on that condition is not appropriately measured, or the clinical trial in which that effect was measured was not appropriately designed.

In deciding whether a proposed clinical entity justifies a new claim, criteria used by the FDA have generally consisted of the following

- The existence of the entity must be broadly accepted by medical experts representing the relevant clinical discipline
- The entity should be operationally definable

If a new claim is sought for a drug that is already approved for a specific indication, a sponsor would be required to establish that the new indication is meaningfully different from the existing claim. Otherwise, the implication in labeling that the 2 indications were different entities when, in fact, they were not, could be considered misleading.

1.4 Current Basis For Approving Drugs For Dementia

In the last 10 years 3 drugs have been approved by the FDA for the treatment of dementia: tacrine, donepezil and rivastigmine. All 3 drugs have been approved for an identical indication: the treatment of mild to moderate Alzheimer's Disease. Their approval has been based upon clinical trials, the key elements of which have been as follows

1.4.1 Diagnosis of Alzheimer's Disease

Patients enrolled in these trials have generally had "probable" Alzheimer's Disease as defined by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Those criteria* are as follows

- Dementia established by clinical examination, and confirmed by a rating scale such as the Mini-Mental Status Examination, and by neuropsychological testing
- Deficits in two or more areas of cognition
- Progressive cognitive worsening
- No disturbance of consciousness
- Onset between ages 40 and 90
- Absence of systemic disorders, and other brain diseases that could account for the progressive cognitive impairment

*The NINCDS-ADRDA criteria for probable Alzheimer's Disease have been shown to be both valid and moderately reliable. They have a sensitivity of > 90%; their specificity is however lower (50 – 60%) and they are particularly lacking in specificity in distinguishing the frontotemporal dementias from Alzheimer's Disease, as well as in distinguishing those who have a combination of cerebrovascular neuropathology and Alzheimer's Disease from those who have pure Alzheimer's Disease.

1.4.2 Severity Of Dementia

Patients enrolled in these trials have been considered to have dementia of mild to moderate severity at study entry. The severity of their dementia has been assessed based on their Mini-Mental Status Examination scores; the range of such scores that have been considered to fit the "mild to moderate" category has been from 10-26.

1.4.3 Design And Duration Of Clinical Trials

These trials have so far invariably been randomized, double-blind, placebo-controlled, parallel-arm studies. The period of double-blind treatment has ranged from 3-6 months.

So far, the approval of drugs for the treatment of Alzheimer's Disease has been based upon demonstrating efficacy in at least 2 such studies, each of at least 3 months' duration.

1.4.4 Outcome Measures For Assessing Drug Efficacy

Draft guidelines issued by this Agency have recommended that the efficacy of putative drugs for dementia be determined using assessments of the following as pre-specified co-primary outcome measures.

- Cognitive functions. The standardized test battery used most widely for this purpose is the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). This battery assesses a spectrum of cognitive functions believed to be impaired in Alzheimer's Disease with each such function being allotted a maximum score; higher scores indicate more severe impairment. The total score for this battery can range from 0 (no impairment) to 70 (severe impairment). Patients with Alzheimer's Disease decline on average 7 to 9 points on this scale every year, although this decline varies widely
- A clinician's overall impression of how the patient's cognition, behavior and function have changed over the course of the study; this has been referred to as a "global" assessment. Several different methods of making such an assessment have been proposed. The most widely used method is the Clinician Interview Based Impression of Change-Plus (CIBIC-Plus). The CIBIC-Plus is based upon information obtained from an interview of the patient and caregiver, and the recall of the patient's earlier condition, by an independent clinician who is blinded to the results of more formal assessments of cognitive function, such as the ADAS-Cog or Mini-Mental Status Examination, carried out by others. The CIBIC-Plus is rated on a scale from 1 (marked improvement) to 7 (marked worsening); a rating of 4 denotes no change.

A cognitive rating scale has been recommended as a primary outcome measure since the core symptoms of dementia are cognitive. However, since the clinical significance of a change on a cognitive rating scale may not be clear, a global

scale has been recommended as a second primary outcome measure. For approval to be granted it has been required that superiority of the drug over placebo be demonstrated separately on each of these 2 types of measures.

For most clinical trials completed over the last 10 years, the ADAS-Cog and CIBIC-Plus have been the primary outcome measures.

1.4.5 Symptomatic Effect Versus Disease Modification

The clinical trials on which the approval of drugs for Alzheimer's Disease have been based have thus far been considered not to be designed to distinguish between a purely symptomatic effect of the drug in question and a disease-modifying effect. In this context, the term "disease-modifying" refers to an effect on the underlying pathology of the disease.

Accordingly, the class labeling for these drugs states: "There is no evidence that -------(name of drug) alters the course of the underlying dementing process."

Two theoretical study designs that have been proposed for making this distinction are further described below. Both designs apply to studies that are randomized, double-blind, placebo-controlled and parallel-arm throughout. Each proposed design has 2 study segments:

- Randomized withdrawal design. In the initial segment patients are randomized to either active drug or placebo. This segment is then allowed to continue for a sufficient duration to allow the active drug to demonstrate efficacy in relation to placebo. At the beginning of the second study segment those randomized to active drug in the initial phase are further randomized to either continue active drug or receive placebo. The second study segment then continues for an appropriate period. If at the end of the second segment, those receiving placebo, in that phase only, maintained their difference from those who received placebo through both segments, a disease-modifying effect would be assumed. On the other hand should those receiving placebo in the second segment only deteriorate to the level of those who received placebo throughout, a purely symptomatic effect would be inferred
- Randomized start design. In the initial segment patients are again randomized to active drug or placebo. This segment is then allowed to continue for a sufficient duration to allow the active drug to demonstrate efficacy in relation to placebo. At the end of that period those who received placebo during the initial segment are re-randomized to receive active drug or placebo for the entire duration of the second segment, as are those who initially received active drug. If at the end of the second segment the group which received placebo initially "catches up" with those who received active drug throughout a symptomatic effect is inferred; on the other hand if a difference between the groups is maintained, the active drug is assumed to have a disease-modifying effect

Both study designs can still be considered theoretical and have yet to be adequately assessed in a clinical trial setting. The appropriate durations of each segment, the frequency of assessments and a number of analytical issues need to be resolved.

The use of brain imaging measures (such as volumetric magnetic resonance imaging of hippocampal and whole brain atrophy) have been proposed as surrogate markers to assess the effects of putative disease-modifying agents in Alzheimer's Disease. While a detailed review of regulatory considerations that pertain to surrogate markers is beyond the scope of this paper, it would be highly desirable for the following questions to be answered prior to such a marker being considered acceptable for use in key clinical trials that are intended to assess the effects of disease-modifying agents in Alzheimer's Disease.

- What clinical outcome is the imaging marker a surrogate for?
- Does the imaging marker reliably predict the desired clinical outcome?
- Is the desired clinical outcome based on the drug effect on the surrogate?

2 Issues For Discussion Regarding Vascular Dementia

Definitive effectiveness drug trial protocols in vascular dementia that we have reviewed have had the following features

- All been randomized, double-blind, placebo-controlled, and parallel-arm in design
- Patients with probable and/or possible vascular dementia by NINDS-ADRDA criteria, and of mild-to-moderate severity have been enrolled
- Trials have been of 6 months' duration
- Active drug treatment arms have had sample sizes between 150 and 400 patients
- Key efficacy measures have consisted of
  - A cognitive measure: ADAS-Cog (standard or extended version)
  - A global measure: CIBIC-Plus or ADCS-CGIC

2.1 Is the entity clearly definable, clinically and pathologically?

When a drug is approved by the Agency for treatment of a specific entity, it is implied that there is broad agreement within the relevant medical discipline(s) that

- such an entity exists
- is sufficiently homogenous
- the condition can be identified by practicing clinicians with a reasonable degree of consistency using accepted operational criteria

In the case of vascular dementia, a basic question is whether that entity constitutes a distinct clinical syndrome, given the heterogeneity of the pathology and clinical features that are reported to underlie that condition. In deciding whether vascular dementia does represent a new distinct clinical syndrome, conventional criteria for determining the clinical validity of such a concept could be used. Such criteria might include

- The existence of a cluster of related symptoms with a characteristic time course, identified by cluster analysis or clinical observation, and
- A distinct separation of the entity of interest from related conditions by discriminant function analysis.

2.2 Are there valid criteria for its diagnosis? Can the entity be distinguished from Alzheimer's Disease and other causes of dementia?

In order to conduct clinical trials of a drug that evaluate its efficacy for a specific indication, criteria should be available for defining that entity so that a sufficiently homogenous population is selected for such trials. Such criteria should ideally have a high degree of sensitivity and specificity when compared with a "gold standard". While the specific diagnostic criteria used in clinical trials may not always be applicable in their entirety to the clinical setting, they should be broadly representative of that entity as identified by a practicing clinician.

For any set of diagnostic criteria that are being proposed for use in clinical trials a high degree of inter-rater reliability is also desirable.

A number of different sets of criteria have been proposed for the diagnosis of vascular dementia. These include the Hachinski Ischemic Scale, and the ADDTC, ICD-10, DSM-IV and NINDS-AIREN criteria. The limited comparative data available seem to suggest that, when these criteria have been compared against pathological findings as the gold standard, their sensitivity and specificity (in differentiating Alzheimer's Disease from vascular dementia) are highly variable. Inter-rater reliability also appears to vary considerably across criteria. The different sets of criteria do not appear to be interchangeable. Indeed, we may fairly ask if it is reasonable to consider vascular dementia (even if it is clinically distinguishable from Alzheimer's Disease [see below]) a single clinical entity, or, whether it is really several distinct entities, defined by significantly different underlying pathologies, and, therefore, whether it is reasonable to grant a "global" claim for "vascular dementia", or whether drug development should target specific sub-types of vascular dementia, each defined by a unique pathology.

An additional problem is that these sets of criteria have been developed by consensus and do not appear to have been individually validated by neuropathological correlation in prospective, community-based studies.

From the limited information available it also appears that most, if not all, these criteria have even less specificity in differentiating pure vascular dementia from mixed forms that have pathological features of both Alzheimer's Disease and cerebrovascular disease; such mixed forms of dementia are not uncommon. It will be critical to determine if so-called "pure" vascular dementia can reliably be differentiated, on clinical grounds, from the mixed forms of dementia, or even "pure" Alzheimer's Disease. Such a lack of specificity is particularly problematical when a claim is made that an intervention that is already established as being effective in Alzheimer's Disease, is also demonstrated to be effective in "vascular dementia", when that entity is defined by any of the above sets of criteria. If these criteria do not differentiate well between pure vascular dementia and mixed forms having features of both vascular dementia and Alzheimer's Disease, it might then need to be determined to what extent any perceived treatment effect in "vascular dementia" is attributable to the effect of that treatment on co-existing Alzheimer's Disease.

A further complicating element in attempting to separate Alzheimer's Disease from vascular dementia is the reported near-universal presence of certain specific vascular lesions in cases of Alzheimer's Disease. These changes include cerebral amyloid angiopathy, degenerative changes in the cerebral microvasculature and abnormalities of the periventricular cerebral white matter such as demyelination and reactive gliosis. A role of such vascular abnormalities in contributing to the dementia syndrome of Alzheimer's Disease has been

postulated, i.e., it has been suggested that in even the more pure forms of Alzheimer's Disease, vascular abnormalities may be responsible, at least in part, for the dementia syndrome. In other words is even the most distinct form of Alzheimer's Disease a vascular dementia, at least in part?

2.3 What outcome measures are appropriate to use in clinical drug trials for vascular dementia? Should clinical trials for this entity have any unique features in their design?

Assuming that vascular dementia can accepted as a distinct clinical syndrome and can be identified with a high degree of sensitivity and specificity for purposes of conducting clinical trials, a number of further questions arise as to the design and conduct of such trials.

One such issue is the choice of outcome measures. Since the core manifestations of any dementing disorder must be cognitive, a validated and reliable cognitive measure should presumably be one of the primary efficacy assessments if the same paradigm that is used for pivotal clinical trials in Alzheimer's Disease is applied to vascular dementia . Such an instrument should ideally sample the entire spectrum of cognitive deficits across the range of disease severity in the population included in the trial, be sensitive to longitudinal change and provide a composite score, as well as have other characteristics. Whether a cognitive assessment battery such as the ADAS-Cog is appropriate for use in vascular dementia is less clear; it is has been suggested for example that frontal lobe function deserves greater attention in a cognitive battery for vascular dementia than is provided by the standard ADAS-Cog .

Again using the same paradigm that is applied to Phase 3 clinical trials for Alzheimer's Disease, it would seem appropriate that an additional primary efficacy measure in vascular dementia should be a global assessment of improvement such as the CIBIC-Plus. Such a global measure would, at least in theory, help confirm that any cognitive change was clinically meaningful.

Based on the known natural history of Alzheimer's Disease and early clinical trials for that condition, it has been recommended that the duration of key efficacy trials for that disease should be at least 3-6 months. Whether a similar duration would be appropriate for a clinical trial in vascular dementia would depend largely on what is known about the natural history of that entity.

A further issue that merits discussion is the overall design of efficacy trials in vascular dementia. Since Alzheimer's Disease is believed to generally have a steadily worsening clinical course, a randomized, double-blind, placebo-controlled, parallel-arm design has been felt to be the most appropriate for that condition. Whether a similar design is appropriate for clinical drug trials in vascular dementia, as may have been assumed, would also be expected to depend on what is known about the natural history of that entity.

Additional items that may merit discussion in the context of this subsection would include

- Sample sizes for clinical trials in vascular dementia based on what is known about the natural history of that putative disorder, efficacy data from pilot studies in vascular dementia, drug effects in other types of dementia, and what might be considered a desirable clinical effect
- Study designs that might help distinguish between disease-modifying effects (that are distinct from the prevention of discrete strokes) and symptomatic effects

In this memo, we have outlined the issues we would like the Committee to discuss in advising the Division about the development of treatments for the entity referred to as Vascular Dementia. Of course, we are eager to hear your views not only on the issues we have identified, but on any other issue you believe to be relevant. We very much appreciate your thoughts on this matter, and look forward to seeing you and to a lively discussion.